REMARKS

Applicants believe that the amendments provide herewith the Renewed Notice To Comply With The Sequence Rules, as sequence identifies have now been inserted at locations where figure numbers were previously located as identification of particular amino acid or nucleic acid sequences. Applicants believe that full compliance with the rules has now been achieved, and accordingly, an early action on the merits is now believed to be in order and is courteously solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 2 on page 4 has been amended as follows:

According to the present invention there is provided a tissue cement protein having the amino acid sequence shown in Figure 3 (SEQ ID NO: 11) or Figure 7 (SEQ ID NO: 16) or containing any one of the partial amino acid sequences shown in any one of Figures 2 (SEQ ID NO: 1), 4 to 6 (SEQ ID NOS: 3, 6 and 14) and 8 (SEQ ID NO: 17), related tissue cement proteins from blood-feeding parasites, preferably ticks, and functional equivaients thereof.

Paragraph beginning at line 16 on page 4 has been amended as follows:

The term "functional equivalents" is used herein to describe those proteins that have an analogous function to tissue cement proteins containing the amino acid sequences identified in any one of Figures 2 to 8 (SEQ ID NOS: 1, 3, 6, 11, 14, 16 or 17).

Paragraph beginning at line 20 on page 4 has been amended as follows:

These proteins may belong to the same protein family as the proteins and partial proteins identified in Figures 2 to 8 (SEQ ID NOS: 1, 3, 6, 11, 14, 16 or 17). By protein family is meant a group of polypeptides that share a common function and exhibit common sequence homology between motifs present in the polypeptide sequences.

Paragraph beginning on line 14, on page 6, has been amended as follows:

It is thought that most of the protein and partial protein sequences so far identified and shown in Figures 2 to 8 (SEQ ID NOS: 1, 3, 6, 11, 14, 16 or 17) are structural components of tissue cement. The applicant, however, does not wish to be bound by this theory. For example, the protein sequence identified in Figure 2 (SEQ ID NO: 1) appears to contain a signal sequence and its sequence resembles that of keratin, a widely studied structural protein. Similarly, the protein whose sequence is set out in Figure 3 (SEQ ID NO: 11) also contains a signal sequence and is glycine and proline rich, like many structural proteins. The cemA protein, whose partial sequence is illustrated in Figure 4 (SEQ ID NO: 3), contains a number of repeats and is thus also likely to be a structural component of tissue cement.

Paragraph beginning at page 6, line 24, has been amended as follows:

The protein of Figure 5 (SEQ ID NO: 6) is composed of a number of repeats and resembles collagen in sequence. The encoding cDNA shares sequences in common with glutenin, a known self-assembling protein. It thus seems likely that this protein is capable of self-assembly. The applicant, however, does not wish to be bound by this theory. The possibility that this particular sequence may be involved in self-assembly raises the opportunity of using these motifs to bestow on an unrelated protein the ability to self-assemble.

Paragraph beginning at page 7, line 1, has been amended as follows:

In common with some of the other proteins illustrated in the accompanying Figures, the

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protein of Figure 6 (SEQ ID NO: 14) contains a number of consensus recognition sites for carbohydrate moieties, in particular glycosaminoglycans.

Paragraph beginning at page 7, line 5, has been amended as follows:

The protein sequence illustrated in Figure 7 (SEQ ID NO: 16) also contains consensus attachment sites for glycosaminoglycan moieties and possesses a putative signal sequence. The amino terminal half of the protein resembles collagen, whilst the carboxy terminal shares more in common with keratin. The protein is glycine-rich and contains several repeats of the motif (C/S)l-4(Y/F) which is also found in structural proteins from the egg shells of certain insects. The tyrosines in these consensus sequences may be involved in the cross-linking of this protein through the formation of dityrosine bridges by the action of phenoloxidases.

Paragraph beginning at page 7, line 14, has been amended as follows:

The sequence of Figure 8 (SEQ ID NO: 17) is both glycine and tyrosine rich and resembles a cement protein of the reef-building polychaete *Pragmatopoma californica* (see Figure 9) (SEQ ID NO: 9). It is thus likely that this protein is also a structural component of tissue cement. The applicant, however, does not wish to be bound by this theory.--

Paragraph beginning at page 15, line 28, has been amended as follows:

According to a further aspect of the present invention there is provided a nucleic acid molecule encoding a tissue cement protein as defined above, or any functionally equivalent form.

The nucleic acid sequences of choice comprise or contain the nucleic acid sequences exhibited in Figures 2 to 8 (SEQ ID NOS: 2, 4, 5, 7, 12, 13 or 15). The skilled man will appreciate that changes may be made at the nucleotide level by addition, substitution, deletion or insertion of one or more nucleotides, which changes may or may not be reflected at the amino acid level, dependent on the degeneracy of the genetic code.

Paragraph beginning at page 16, line 30, has been amended as follows:

Accordingly, antisense sequences for use in accordance with this aspect of the present invention comprise sequences that hybridise under standard conditions to the nucleic acid sequences exhibited in Figures 2 to 8 (SEQ ID NOS: 2, 4, 5, 7, 12, 13 or 15). Hybridising sequences' included within the scope of the invention are those binding under standard conditions. As used herein, by 'standard conditions' is meant both non-stringent hybridisation conditions (6 x SSC/50% formamide at room temperature) with washing under conditions of low stringency (2 x, room temperature, or 2 x SSC, 42°C) or at standard conditions of higher stringency, e.g. 2 x SSC, 65°C (where SSC = 0.15M NaCl, 0.015M sodium citrate, pH 7.2). Preferably standard conditions refers to conditions of high stringency.

Paragraph beginning at page 19, line 15, has been amended as follows:

Figure 2 is a partial cDNA sequence (SEQ ID NO: 2) and translation product (SEQ ID NO: 1) of clone 21. The cDNA-inferred protein is a cement protein; it contains a hydrophobic N-terminal region which possibly constitutes a signal sequence, typical for secreted proteins. The

protein strongly resembles other structural proteins. especially keratin. A recognition sequence for post-translational attachment of glycosaminoglycan groups is underlined.

Paragraph beginning at page 19, line 21, has been amended as follows:

Figure 3 is the cDNA (SEQ ID NO: 5) and cDNA-inferred polypeptide sequence (SEQ ID NO: 11) of clone 33. A putative signal sequence is given in bold. Like many structural proteins, this protein is glycine- and proline-rich. The protein also displays some resemblance to keratins.

Paragraph beginning at page 19, line 25, has been amended as follows:

Figure 4 is a partial sequence of *cemA* cDNA (SEQ ID NO: 12) and the cDNA-inferred polypeptide sequence (SEQ ID NO: 3). The protein is very repetitive, with the sequence KGALLQQQQASQVKGALKAI, or slight variants thereof, repeated several times.

Paragraph beginning at page 19, line 29, has been amended as follows:

Figure 5 is a partial cDNA (SEQ ID NO: 4) and cDNA-inferred polypeptide sequence (SEQ ID NO: 6) of clone 24. The protein has resemblance to structural proteins (amongst others collagen), and [is] contains repeats. The cDNA also has a region in common with glutenin, a self-assembling protein.

Paragraph beginning at page 20, line 1, has been amended as follows:

Figure 6 is a partial cDNA (SEQ ID NO: 13) and cDNA-inferred sequence (SEQ ID NO:

14) of clone 68. The encoded proteins resemble structural proteins, such as keratin. A series of putative glycosaminoglycan attachment sites are underlined.

Paragraph beginning at page 20, line 6, has been amended as follows:

Figure 7 is the complete cDNA sequence (SEQ ID NO: 15) and cDNA-inferred polypeptide sequence (SEQ ID NO: 16) of clone 64. The putative signal sequence is give in bold. A possible glycosaminoglycan attachment site is underlined. The first 40 amino-acid section of the mature protein is collagen-like, whilst the remainder of the sequence resembles keratin. The protein is glycine-rich and contains several repeats of the motif (C/S)1-4(Y/F), which is also found in structural proteins from insect egg shells. The tyrosines may be involved in cross-linking by formation of dityrosine-bridges by phenoloxidases. A similar protein is encoded by clone I (see Figure 8).

Paragraph beginning at page 20, line 15, has been amended as follows:

Figure 8 is a partial cDNA-sequence (SEQ ID NO: 7) and cDNA-inferred polypeptide sequence (SEQ ID NO: 17) of clone I. The inferred protein is glycine- and tyrosine-rich and resembles a cement protein of the reef-building polychaete *Pragmatopoma califomica* (a component of the quinone-tanned cement in the tubes built by these marine worms).

Paragraph beginning at page 20, line 20, has been amended as follows:

Figure 9 is a DNA alignment between the protein sequence shown in Figure 8 (SEQ ID

NO: 8) and a cement protein from the polychaete *Pragmatopoma californica* (SEQ ID NO: 9).

Paragraph beginning at page 23, line 28, has been amended as follows:

A number of clones were sequenced or partially sequenced. The sequences or partial sequences of those clones are shown in Figures 2 to 8 (SEQ ID NOS: 2, 4, 5, 7, 12, 13 or 15) attached hereto. Explanations of the structure and features of the cloned sequences are given in the Brief description of the Figures above and in other parts of the description.

Paragraph beginning at page 28, line 14, has been amended as follows:

Oligonucleotides with appropriate restriction enzyme sites were designed to permit PCR cloning of an N-terminal fragment of clone 64, as shown in Figure 7 (SEQ ID NO: 16). This fragment, known as 64P (amino acids 34 to 85) from the cDNA, was PCR cloned in-frame into the pET23 vector (Novagen). The construct, 64TRP (encoding amino acids 34 to 85), tagged onto the 6 x His-Tag of the pET23 vector, was obtained using standard PCR cloning methods (Sambrook *et al.,* 1989). The plasmid was transformed into *E. coli* AD494 cells (Sambrook *et al.,* 1989).

In the Claims:

Claim 1 has been amended as follows:

1. (Amended) A tissue cement protein having the amino acid sequence shown in [Figure 3] SEQ ID NO. 11 or [Figure 7] SEQ ID NO. 16 or containing any one of the partial amino acid sequences shown in any one of [Figures 2, 4 to 6 and 8] SEQ ID NOS. 1, 3, 6, 14 or 17, related tissue cement proteins from blood-feeding parasites, preferably ticks, and functional equivalents thereof.